



Association of Amplitude Spectral Area of the Ventricular Fibrillation Waveform With Survival of Out-of-Hospital Ventricular Fibrillation Cardiac Arrest

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ABSTRACT

BACKGROUND Previous investigations of out-of-hospital cardiac arrest (OHCA) have shown that the waveform characteristic amplitude spectral area (AMSA) can predict successful defibrillation and return of spontaneous circulation (ROSC) but has not been studied previously for survival.

OBJECTIVES To determine whether AMSA computed from the ventricular fibrillation (VF) waveform is associated with pre-hospital ROSC, hospital admission, and hospital discharge.

METHODS Adults with witnessed OHCA and an initial rhythm of VF from an Utstein style database were studied. AMSA was measured prior to each shock and averaged for each subject (AMSA-avg). Factors such as age, sex, number of shocks, time from dispatch to monitor/defibrillator application, first shock AMSA, and AMSA-avg that could predict pre-hospital ROSC, hospital admission, and hospital discharge were analyzed by logistic regression.

RESULTS Eighty-nine subjects (mean age 62 ± 15 years) with a total of 286 shocks were analyzed. AMSA-avg was associated with pre-hospital ROSC ($p = 0.003$); a threshold of 20.9 mV-Hz had a 95% sensitivity and a 43.4% specificity. Additionally, AMSA-avg was associated with hospital admission ($p < 0.001$); a threshold of 21 mV-Hz had a 95% sensitivity and a 54% specificity and with hospital discharge ($p < 0.001$); a threshold of 25.6 mV-Hz had a 95% sensitivity and a 53% specificity. First-shock AMSA was also predictive of pre-hospital ROSC, hospital admission, and discharge. Time from dispatch to monitor/defibrillator application was associated with hospital admission ($p = 0.034$) but not pre-hospital ROSC or hospital discharge.

CONCLUSIONS AMSA is highly associated with pre-hospital ROSC, survival to hospital admission, and hospital discharge in witnessed VF OHCA. Future studies are needed to determine whether AMSA computed during resuscitation can identify patients for whom continuing current resuscitation efforts would likely be futile. (J Am Coll Cardiol 2014;64:1362-9) © 2014 by the American College of Cardiology Foundation.

Based on data from the Resuscitation Outcomes Consortium, out-of-hospital cardiac arrest (OHCA) treated by emergency medical services (EMS) is estimated at 424,000 cases per year, of which approximately one-fourth have an initial shockable rhythm, ventricular fibrillation (VF), or ventricular tachycardia (1). Survival to hospital discharge in 2011 was 10.4% overall but 31.7% for

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Manuscript received January 12, 2014; revised manuscript received May 29, 2014, accepted June 3, 2014.



witnessed VF (1). Some of the modifiable factors that are associated with improved survival include the performance of high-quality cardiopulmonary resuscitation, including chest compression depth (2,3); chest compression rate between 100 and 120 compressions per minute (4); minimization of preshock pauses in chest compressions (5); and use of an automated external defibrillator prior to arrival of EMS (6,7). Although such factors remain critically important to helping improve the performance of CPR, rescuers also need guidance to assess when further efforts are futile and resuscitation should be changed or terminated.

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Amplitude spectral area (AMSA), which reflects the summed product of VF frequency and signal amplitude, correlates with coronary perfusion pressure during chest compressions (8,9) and with myocardial energy phosphate concentrations (10). Furthermore, AMSA has been shown to predict defibrillation and return of spontaneous circulation (ROSC) in both animal (11-13) and human cardiac arrest studies (14-16). The relationship of AMSA to longer-term outcomes, such as survival to hospital admission or discharge, has been mostly unknown, although a recently published study demonstrated a connection between AMSA and survival with good neurological outcome (17). We hypothesized that the average value of AMSA measured prior to a defibrillation shock would predict attainment of pre-hospital ROSC, survival to hospital admission, and survival to hospital discharge in patients with OHCA with witnessed initial rhythm of VF.

METHODS

Resuscitation data from adult patients with bystander-witnessed OHCA were collected through the Saving Hearts in Arizona Registry and Education (SHARE) program, a statewide Utstein style database described previously (18). OHCA was designated a major public health problem by the Arizona Department of Health Services, and SHARE was created to measure response to OHCA and improve outcomes. Thus, SHARE program initiatives and its data collection are exempt from the Health Insurance Portability and Accountability Act. By virtue of SHARE being a health department-sponsored public health initiative, the Arizona Department of Health Services' Human Subjects Review Board and the University of Arizona institutional review board have determined that neither the interventions nor their evaluation constitutes human subjects research and have approved the publication of de-identified data.

Data for this investigation were taken from 2 sites in Arizona participating in the SHARE program, from 2008 through 2011. Details of the methodology for data collection in the SHARE database have been described previously (18,19). Inclusion criteria were OHCA with resuscitation initiated in the field. Exclusion criteria included age <18 years old, unwitnessed arrest, or initial rhythm other than VF. ROSC was defined as a confirmed pulse for at least 5 minutes.

Electronic waveform data were recorded from the defibrillator pads to an E series monitor/defibrillator (ZOLL Medical Corp., Chelmsford, Massachusetts) at a sampling rate of 250 samples/s, then downloaded to an American Standard Code for Information Interchange (ASCII) file and analyzed with customized software (Matlab, Mathworks, Natick, Massachusetts). A time segment of ventricular fibrillation of 4.1 s (N = 1,024 data points) was chosen prior to each shock, occurring within 10 s of that shock and visually free of artifacts including chest compressions. (Emergency medical personnel were not instructed to deliberately hold compressions.) Prior to computation of AMSA, the signal was first filtered using a discrete Fourier transform on the consecutive data points for positive frequencies up to 50 Hz; of note, this step consequently reduces the voltage by a factor of 2. A second discrete Fourier transform was then performed on all 1,024 data points (no zero padding) to determine amplitude at each frequency (A_i), computed as the absolute value of signal intensity (i.e., power) at that frequency and divided by the square root of N. AMSA was then computed as the summed product of frequency (F_i) and amplitude (A_i) over a frequency interval of 4 to 48 Hz (resolved in frequency steps of 250/N Hz), as $AMSA = (1/N) \sum_i A_i \times F_i$.

This formulation provides the advantage of yielding stable and consistent values of AMSA, even if computed for an N other than 1,024 (i.e., 512 or 2,048 data points). We chose the frequency range from 4 to 48 Hz in accordance with other published studies (12,20), although AMSA has been reported using lower frequency limits of 2 Hz (14) and 3 Hz as well (21,22). AMSA was then averaged over all shocks within that subject (AMSA-avg). In a subject with only 1 shock, AMSA-avg by definition was equal to the value of the first shock AMSA. The average of AMSA was chosen to allow for an overall representation of the VF waveform as AMSA values can vary over time. AMSA prior to the first shock ($AMSA_1$) was also analyzed. Figure 1 shows examples of a VF waveform with an AMSA

ABBREVIATIONS AND ACRONYMS

AMSA = amplitude spectral area

AUC = area under the curve

EMS = emergency medical services

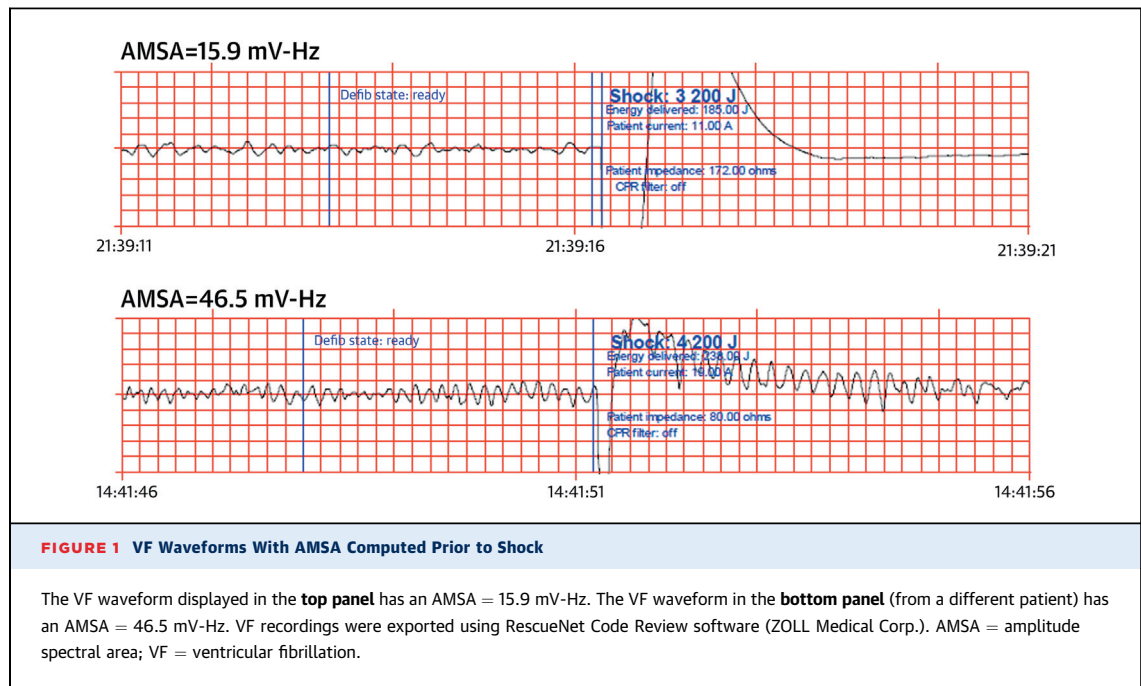
OHCA = out-of-hospital cardiac arrest

ROC = receiver operator characteristic

ROSC = return of spontaneous circulation

SHARE = Saving Hearts in Arizona Registry and Education program

VF = ventricular fibrillation

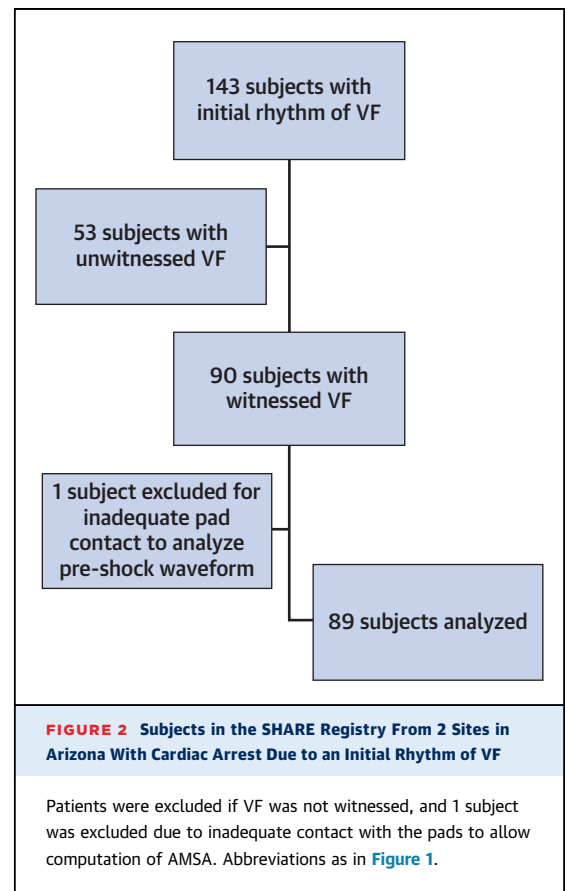


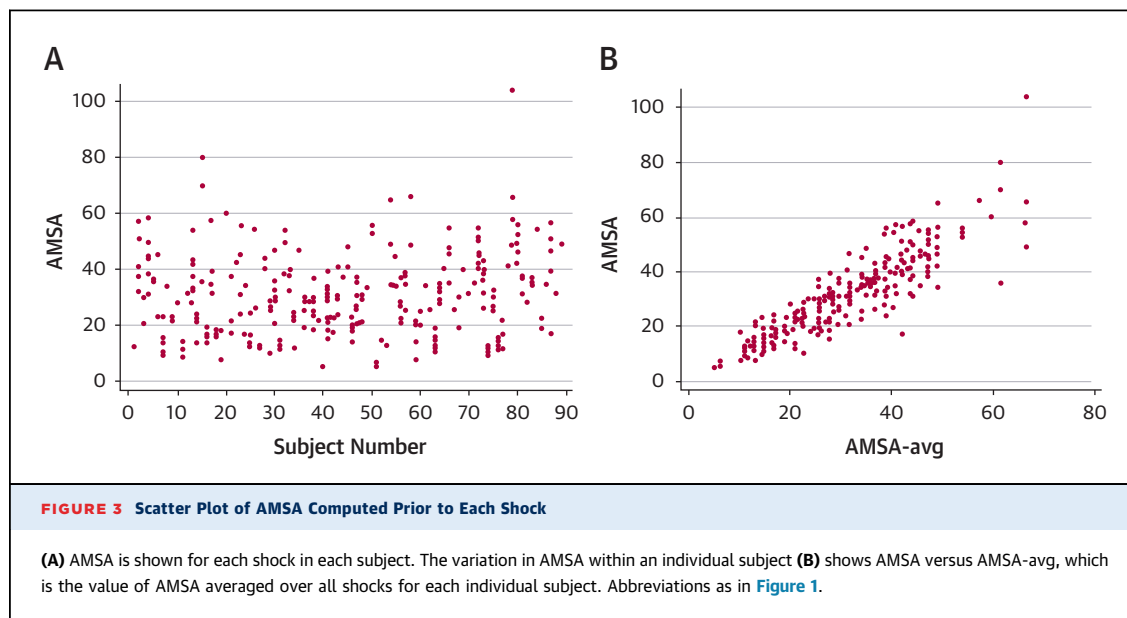
value of 15.9 mV-Hz and a VF waveform with an AMSA value of 46.5 mV-Hz. (VF recording was exported using RescueNet Code Review software, ZOLL Medical Corp.)

STATISTICS. Data are mean ± SD. Logistic regression was performed to determine factors predictive of 3 resuscitation outcomes: pre-hospital ROSC, hospital admission, and hospital discharge. Factors analyzed included age, sex, number of shocks, time from EMS dispatch to connection of the monitor/defibrillator, AMSA_i, and AMSA-avg. Factors with a p value of <0.1 in univariate analysis were then tested in a multivariate analysis, with a p value of 0.05 selected for significance. (As AMSA_i and AMSA-avg are highly correlated, they were not tested together in the multivariate analysis.) A receiver-operator characteristic (ROC) curve analysis was performed to determine sensitivity and specificity of AMSA-avg to predict resuscitation outcome. Data were analyzed with Stata version 10.0 software (StataCorp LP, College Station, Texas).

RESULTS

A total of 89 adult OHCA cases with witnessed VF from the SHARE database were studied, including 69 men and 20 women (**Figure 2**). One subject was excluded because pad contact was inadequate for obtaining a clear signal to compute pre-shock AMSA. A total of 286 shocks were analyzed, with a





median of 2 shocks per subject and 17 subjects having only 1 shock. Mean time from EMS dispatch to connection of the monitor/defibrillator was 7.0 ± 2.7 min. Figure 3 shows AMSA values prior to each shock and for each subject indexed by subject number (Figure 3A) and by AMSA-avg for that subject (Figure 3B). Pre-hospital ROSC was attained in 41 subjects (46%), hospital admission in 52 subjects (58%), and hospital discharge in 34 subjects (38%). Table 1 summarizes patient and resuscitation characteristics.

According to the univariate analyses for resuscitation outcome (Table 2), AMSA-avg was highly significant for predicting pre-hospital ROSC ($p = 0.003$), hospital admission ($p < 0.001$), and hospital discharge ($p = 0.001$). Similarly, AMSA₁ was predictive of pre-hospital ROSC ($p = 0.025$), hospital admission ($p = 0.002$), and hospital discharge ($p = 0.001$). Age, sex, and number of shocks did not portend any of the 3 resuscitation outcomes. Time from EMS dispatch to the connection of the monitor/defibrillator predicted hospital admission ($p = 0.065$) but not hospital discharge or pre-hospital ROSC (Table 2). In the multivariate analysis of hospital admission, AMSA-avg remained highly significant ($p < 0.001$), and time from EMS dispatch to connection of the monitor/defibrillator was marginally significant ($p = 0.034$).

An ROC analysis was performed for AMSA-avg. For pre-hospital ROSC, the area under the curve (AUC) was 0.704. For a sensitivity of 95% to predict pre-hospital ROSC, the AMSA-avg threshold was 20.9 mV-Hz,

giving a specificity of 43.4%, a positive predictive value of 59%, and a negative predictive value of 90.5%; patients with pre-hospital ROSC had a median AMSA-avg of 34.5 mV-Hz compared to 25.1 mV-Hz in patients without pre-hospital ROSC (Figure 4). For hospital admission, AMSA-avg showed an AUC = 0.738; for a 95% sensitivity the AMSA-avg threshold was 21 mV-Hz with a specificity of 54%, a positive predictive value of 74.2%, and a negative predictive value of 86.9%; patients with survival to hospital admission demonstrated a median AMSA-avg of 34.8

TABLE 1 Patient and Resuscitation Characteristics for Trial Subjects (n = 89)

Age, yrs	62 ± 15
Women	22
Age of women, yrs	59 ± 14
Age of men, yrs	63 ± 13
Cardiac cause	95
Time from dispatch to connection of monitor/defibrillator, min	7.0 ± 2.7
AMSA ₁ , mV-Hz	31.0 ± 14.7
AMSA-avg, mV-Hz	31.0 ± 13.4
Number of shocks	286
Number of shocks/patient	2 (1-11)
Outcomes	
Pre-hospital ROSC	41 (46)
Hospital admissions	52 (58)
Hospital discharges	34 (38)

Values are mean ± SD, %, median (range), or n (%), unless otherwise noted.
AMSA = amplitude spectral area; ROSC = return of spontaneous circulation.

TABLE 2 Univariate Predictors of Resuscitation Outcome			
Variable	Pre-Hospital ROSC	Hospital Admission	Hospital Discharge
Age			
p Value	0.665	0.995	0.121
OR (95% CI), per year	0.994 (0.966–1.022)	0.999 (0.972–1.029)	0.977 (0.948–1.006)
Sex			
p Value	0.981	0.638	0.693
OR (95% CI), female-male	1.013 (0.367–2.804)	1.286 (0.452–3.657)	1.231 (0.438–3.453)
Number of shocks			
p Value	0.168	0.585	0.593
OR (95% CI), per shock	0.867 (0.709–1.062)	1.055 (0.869–1.283)	1.054 (0.868–1.281)
Dispatch-monitor/defibrillator connection			
p Value	0.668	0.065	0.155
OR (95% CI), per s	0.999 (0.997–1.002)	0.997 (0.994–1.000)	0.997 (0.994–1.000)
AMSA ₁			
p Value	0.025	0.002	0.001
OR (95% CI), per mV-Hz	1.036 (1.004–1.069)	1.058 (1.021–1.098)	1.061 (1.025–1.099)
AMSA-avg			
p Value	0.003	<0.001	0.001
OR (95% CI), per mV-Hz	1.058 (1.020–1.097)	1.076 (1.033–1.121)	1.070 (1.029–1.112)
AMSA = amplitude spectral area; CI = confidence interval; OR = odds ratio; ROSC = return of spontaneous circulation.			

mV-Hz compared to 20.9 mV-Hz in patients who did not survive to hospital admission (Figure 5). For hospital discharge, the AUC = 0.749 and at a 95% sensitivity the AMSA-avg threshold was 25.6 mV-Hz, giving a specificity of 53%, a positive predictive value of 55.2%, and a negative predictive value of 93.5%; patients with survival to hospital discharge had a median AMSA-avg of 36.1 mV-Hz compared to

25.2 mV-Hz in patients who did not survive to hospital discharge (Figure 6).

DISCUSSION

This study demonstrated a highly significant relationship between AMSA, a VF waveform parameter, and survival from witnessed OHCA with initial rhythm of VF. This investigation suggests that if AMSA is measured during resuscitation it could be used to determine whether continuing the current resuscitation efforts would likely be fruitless.

In swine studies of VF cardiac arrest, AMSA was strongly predictive of ROSC (11-13). Human studies of OHCA with VF also have demonstrated a relationship between the pre-shock VF waveform and shock outcome. In Taiwan, an analysis of the first shock in 155 patients with OHCA and VF showed that AMSA and a VF parameter that measures the waveform’s fractal properties could predict shocks that defibrillated VF to an organized rhythm (22). In a study of 44 OHCA VF patients in Wisconsin, 98 shocks were analyzed for AMSA in relationship to shock outcome and according to whether VF was recurrent or had failed to defibrillate from the previous shock (i.e., shock-resistant VF) (16). The study found that AMSA was higher in shocks delivered for recurrent VF than in shock-resistant VF and that AMSA predicted defibrillation only for shocks delivered for shock-resistant VF.

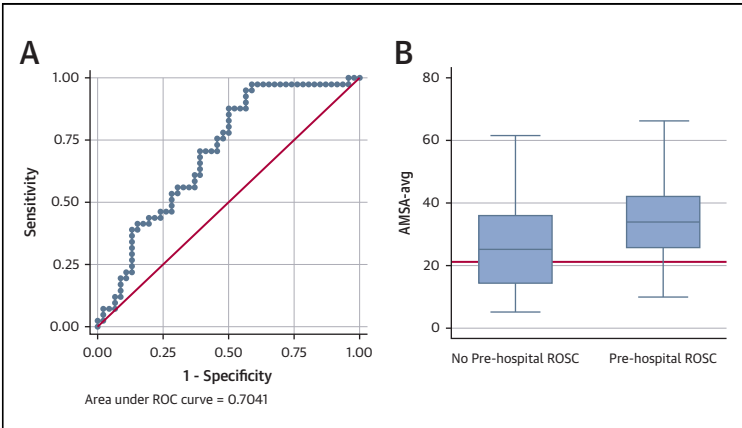


FIGURE 4 AMSA-avg and Achievement of Pre-Hospital ROSC

(A) ROC analysis for AMSA-avg is shown. The area under the curve (AUC) was 0.704. (B) Boxplot of AMSA-avg according to outcome (pre-hospital ROSC). For a sensitivity of 95% to achieve pre-hospital ROSC, the AMSA-avg threshold was 20.9 mV-Hz (red line), yielding a specificity of 43.4%, a positive predictive value of 59%, and a negative predictive value of 90.5%. AMSA = amplitude spectral area; ROC = receiver operator characteristic; ROSC = return of spontaneous circulation.

Other studies (Central Illustration) have considered whether AMSA can predict a perfusing rhythm after shock. In a study of 90 patients receiving 210 shocks, AMSA was greater prior to shocks that resulted in a perfusing rhythm of at least 30 seconds (14); an analysis of 83 patients with OHCA due to VF in Japan showed AMSA was higher in shocks that led to ROSC (23). Finally, in a larger study of 197 patients in Norway that analyzed 770 shocks, investigators determined that slope (a VF parameter analogous to AMSA computed from the time domain signal) predicted ROSC, which occurred following 60 shocks (15).

Although these earlier studies examined outcome immediately related to a specific shock, such as defibrillation or ROSC, it has been unclear whether AMSA may have predictive utility for longer-term outcomes, namely hospital admission and discharge. Such an analysis is now feasible as survival from OHCA with VF has improved greatly in the past few years to 31.7% for witnessed VF in 2011 (1). A recently published investigation analyzed a cohort of 390 patients with out-of-hospital VF arrest and determined that AMSA measured prior to the first shock was associated with good neurological outcome, which occurred in 44.4% of the cohort (17). Our investigation confirms these findings that AMSA is strongly related to hospital discharge, occurring in 38% of this cohort, and furthermore suggests a cutoff may exist below which survival to hospital discharge is highly unlikely (Figure 6).

As VF progresses untreated, AMSA decreases steadily (24-26), which may reflect declines in myocardial energy phosphate concentrations, given that AMSA has been found in a swine model to correlate with adenosine triphosphate concentration (10). AMSA also correlates with coronary perfusion pressure during chest compressions, and this may explain the rise in AMSA that can be seen during resuscitation (11,12,17) and its power to predict defibrillation and ROSC, as higher coronary perfusion pressure values have been related to successful resuscitation in human cardiac arrest (27) and animal models (8,28,29).

It remains unclear whether changes in AMSA track outcomes due to interventions given during resuscitation, such as drugs. In a swine model of ischemia-induced VF, pretreatment with metoprolol, but not labetalol, improved ROSC, yet both agents reduced AMSA compared to controls (25). In a rat model, ranolazine increased AMSA and resulted in an improved resuscitation outcome (30). We have not specifically explored the role of medications given during resuscitation or their effects upon AMSA in this population. Other important questions that warrant further study include whether AMSA may guide

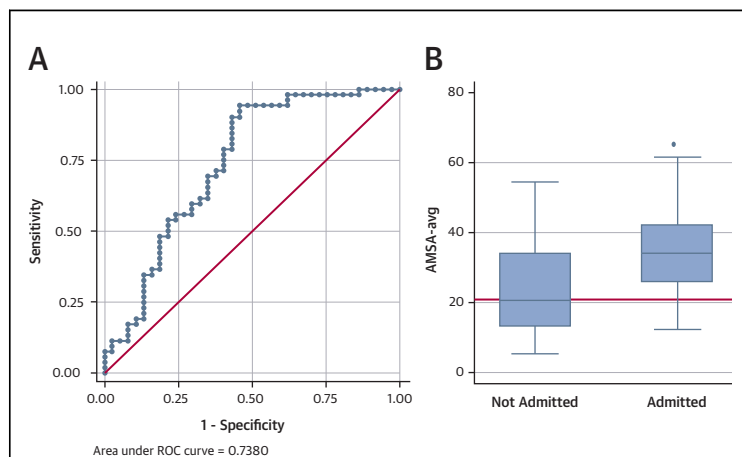


FIGURE 5 AMSA-avg and Achievement of Hospital Admission

(A) ROC analysis for AMSA-avg is shown. The AUC was 0.738. (B) Boxplot of AMSA-avg according to outcome (hospital admission). For a sensitivity of 95% to achieve hospital admission, the AMSA-avg threshold was 21 mV-Hz (red line), yielding a specificity of 54%, a positive predictive value of 74.2%, and a negative predictive value of 86.9%. Abbreviations as in Figure 4.

decisions on the administration of antiarrhythmic drugs or other interventions, in addition to decisions on timing of defibrillation, particularly in refractory VF.

We chose the average of AMSA over shocks to represent the overall VF waveform content. Nonetheless, AMSA of the first shock alone was also highly predictive of outcome, and this likely reflects the

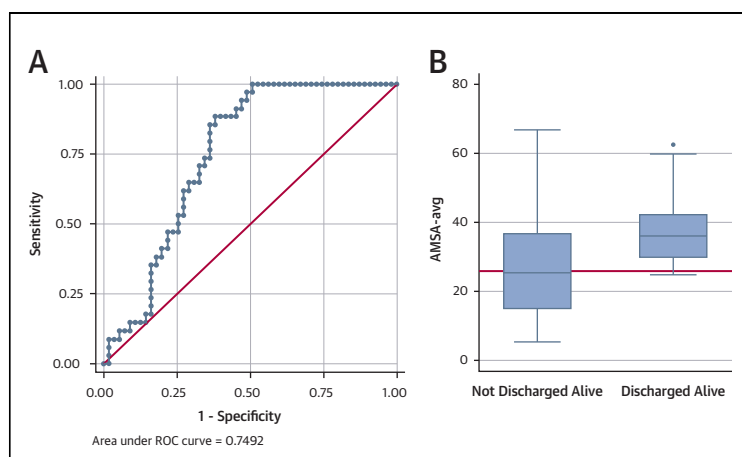


FIGURE 6 AMSA-avg and Survival to Hospital

(A) ROC analysis for AMSA-avg. The AUC was 0.749. (B) Boxplot of AMSA-avg according to outcome (hospital discharge). For a sensitivity of 95% to survive to hospital discharge, the AMSA-avg threshold was 25.6 mV-Hz (red line), yielding a specificity of 53%, a positive predictive value of 55.2%, and a negative predictive value of 93.5%. Abbreviations as in Figure 4.

Study (Year)	Population Studied	N	Endpoints	Findings
Lin et al. (2010) (22)	OHCA	155	Successful defibrillation of first shock	AMSA predictive of defibrillation ($p=0.028$)
Shanmugasundaram et al. (2012) (16)	OHCA, witnessed and with initial rhythm of VF	44	Successful defibrillation stratified by type of VF (recurrent vs shock-resistant)	98 shocks analyzed; AMSA higher in recurrent VF ($p<0.001$) AMSA predictive of defibrillation in shock-resistant VF ($p<0.001$) but not recurrent VF
Ristagno et al. (2008) (14)	OHCA	90	Successful defibrillation with organized rhythm ≥ 40 bpm for ≥ 30 seconds	210 shocks analyzed; AMSA greater in successful shocks ($p<0.0001$)
Nakagawa et al. (2012) (23)	OHCA	83	Comparison of AMSA values according to post-shock rhythm: ROSC, VF, pulseless electrical activity,	AMSA higher prior to shocks that result in ROSC compared to VF ($p<0.05$) or asystole ($p<0.01$)
Schoene et al. (2014) (17)	OHCA, witnessed and with initial rhythm of VF	390	Favorable neurologic survival at hospital discharge	AMSA measured prior to first shock and the change in AMSA over shocks was associated with favorable neurologic survival: $p<0.001$ for first shock AMSA, $p=0.001$ for change in AMSA from shock 1 to 2, and $p=0.04$ from shock 2 to 3
Our investigation	OHCA with initial rhythm of VF	89	Pre-hospital ROSC, hospital admission and discharge	AMSA-avg and first shock AMSA associated with prehospital ROSC ($p=0.003$), hospital admission ($p<0.001$), and hospital discharge ($p<0.001$)

CENTRAL ILLUSTRATION Resuscitation Investigations of AMSA

Evidence table for AMSA. AMSA = amplitude spectral area; AMSA-avg = AMSA averaged over all shocks within that subject; OHCA = out-of-hospital cardiac arrest; ROSC = return of spontaneous circulation; VF = ventricular fibrillation.

finding that the time variation in AMSA is not excessive, as is visually apparent in **Figure 3B**. Other formulations of AMSA, aside from a simple average or value of the first shock AMSA, may better predict survival.

This investigation has examined witnessed OHCA with an initial rhythm of VF, in order to permit a more comprehensive analysis of predictors of survival, including time from EMS dispatch to connection of the monitor/defibrillator. In a witnessed arrest, the time of EMS dispatch would be expected to be closer to the actual time of onset of cardiac arrest than in an unwitnessed episode. Therefore, this investigation was specifically limited to witnessed arrest only. However, future investigations should examine whether AMSA is predictive of survival in unwitnessed arrests, a cohort where the benefit of a predictor that could identify futility for continuing resuscitation could be even greater.

STUDY LIMITATIONS. We acknowledge the limitations of this study, which is a retrospective analysis of a cohort from 2 sites in Arizona; our results

need to be further validated by analyzing additional cohorts of cardiac arrest victims. Ultimately, it should be tested in a prospective fashion with AMSA measured during resuscitation by using the monitor/defibrillator, using a prespecified sensitivity threshold. As noted previously, we have not explored other formulations of AMSA and a more complex formula that differentially weights AMSA values from later versus earlier shocks may perform better to predict survival.

We also have not analyzed the role of well-performed chest compressions and drug therapy during resuscitation and their effects upon the waveform and resuscitation outcome. The study did not take into account post-resuscitation interventions, such as therapeutic hypothermia. Nonetheless, it is remarkable that a waveform parameter, AMSA, was strongly associated with outcome without the need to account for specific resuscitation and post-resuscitation therapies.

CONCLUSIONS

In OHCA with an initial rhythm of VF, the mean value of AMSA (AMSA-avg) is highly associated with outcome, including pre-hospital ROSC, survival to hospital admission, and survival to hospital discharge. If validated in further studies, AMSA may be useful as a parameter to guide resuscitation, and in particular to determine whether continuing current resuscitation efforts are likely to be futile.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE:

Certain features of the ventricular fibrillation waveform in cases of out-of-hospital cardiac arrest may predict outcomes of cardiopulmonary resuscitation. Low amplitude-spectral area values for frequency and amplitude are associated with a lower likelihood of survival to hospital discharge.

TRANSLATIONAL OUTLOOK: Prospective studies are needed to confirm the predictive value of amplitude-spectral area in patients with unwitnessed cardiac arrest and explore implications for postresuscitation management.

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KEY WORDS cardiopulmonary resuscitation, heart arrest, ventricular fibrillation